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Long-term early development research in congenital heart disease (LEADER-CHD): A study protocol for a prospective cohort observational study investigating the development of children after surgical correction for congenital heart defects during the first three years of life



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Long-term early development research in congenital heart disease (LEADER-CHD): A study protocol for a prospective cohort observational study investigating the development of children after surgical correction for congenital heart defects during the first three years of life

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ABSTRACT

Introduction

Congenital heart disease is the most common birth defect. Studies on the development of children with CHD point towards deficits in motoric, cognitive and language development. However, most studies are cross-sectional and there is a gap in the knowledge concerning developmental trajectories, risk and protective factors and a lack of research concerning environmental predictors. Specifically, no studies have so far considered the importance of early caregiving experiences and child temperament for the development of children with CHD.

Methods

In a single-center prospective cohort study, cognitive, motoric and language development of 180 children after corrective surgery for a simple transposition of the great arteries (TGA), tetralogy of Fallot (TOF) or ventricular septal defect (VSD) will be assessed at ages 12, 24 and 36 months with the Bayley Scales of Infant Development 3-d Edition (BSID-III). At age 12 months, a free-play video observation will be conducted to investigate the relationship between primary caregiver and child, and child temperament will be assessed with the Infant Behavior Questionnaire - Revised Short Version (IBQ-R-SV). Medical information will be obtained from patient records, demographic information via questionnaires.

Analysis

Frequency and severity of developmental delays will be reported descriptively. Differences between groups (TGA, TOF, VSD) will be subjected to repeated measure analysis across time points. Multiple regressions will be applied for the analysis of predictors at each time point. For the analysis of differential developmental trajectories, mixed model analysis will be applied.

Ethics and dissemination

The study has been approved by the local medical ethics committee. Written informed consent will be obtained from all participants. Parents have the option to be debriefed about BSID-III results after each assessment and about the study results after project completion. Results will be disseminated in peer-reviewed journals.

Trial registration

The study was prospectively registered with the German Clinical Trials Register.

STRENGTH AND LIMITATIONS OF THIS STUDY

- No brain MRI will be conducted at any time point; postnatal MRI of the brain might provide valuable insights into the relationship between alterations of the central nervous system, perioperative complications and developmental delays, but is beyond the scope of this study.
- The longitudinal study design allows the investigation of developmental trajectories across different time points and of specific predictors for differential trajectories.
- By investigating 3 CHD groups (TGA, TOF, VSD), valuable information can be derived for distinctive patterns of development dependent on diagnosis.
- To our knowledge, this interdisciplinary study is the first to investigate the role of quality of caregiver-child interaction for development in this patient group, which has important theoretical implications and is highly relevant for the development of secondary prevention programs.

KEY WORDS

Congenital Heart Disease, Transposition of the Great Arteries, Tetralogy of Fallot, Ventricular Septal Defect, Cyanotic Heart Defect, Acyanotic Heart Defect, Development, Motoric Development, Language Development, Cognitive Development, Parenting, Temperament, Quality of Caregiving, Primary Caregiver

INTRODUCTION

Background and rationale

1
2
3 Congenital heart disease (CHD) is the most common birth defect and the incidence ranges
4 from 19 to 75 per 1000 live births worldwide[1]. During the past years, medical care for
5 children with CHD has significantly improved, due to scientific progress leading to
6 advancement of early diagnostics[2-5] and technical possibilities[6, 7]. This has led to
7 increased survival rates[8, 9]. In Germany, more than 6500 children are born with a CHD
8 each year, which is approximately every hundredth child, and more than 90% reach
9 adulthood, while mortality has fallen by 60% since 1990[10]. There is now a growing
10 research interest in morbidity and quality of life of these patients[11, 12]. Studies on the
11 development of children with CHD generally point towards deficits in motoric, cognitive and
12 language development[13-18], which are mostly weak to moderate and often combined[19].
13 Even though developmental delays tend to decline with time[13], they are still observed
14 many years after successful surgery and potentially manifest themselves in learning or
15 behavioral difficulties[20, 21], which implies that they are not transient in nature. Children
16 with cyanotic heart defects, such as transposition of the great arteries (TGA) or tetralogy of
17 Fallot (TOF) have been found to have worse developmental outcomes than children with
18 acyanotic heart defects, such as ventricular septal defects (VSD), in several studies[22-26],
19 while other studies did not find systematic differences between TGA, TOF, or VSD, for
20 instance after taking demographic, preoperative, and operative variables into account[15].
21 These contrasting results point towards a complex relationship between physiological
22 characteristics of the heart defect, neurological sequelae, therapeutic necessities and
23 patient-related factors when it comes to future development[27, 28].

24
25 On a neurological level, the etiology of developmental delays in children with CHD is
26 complex, concerning the specific time point as well as the mechanism that leads to
27 alterations[29]. Already pre-operatively, certain abnormalities of the central nervous system
28 can be observed, in particular less mature macro- and microstructural brain development and
29 lower brain volume[28]. These changes can be attributed to reduced oxygenation and
30 perfusion, while the relative contribution depends on the specific defect[30]. Decelerated
31 brain development is a predisposing factor for white matter injury, which is often present in
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newborns with CHD[31]. In addition, infarction, ischemic strokes and cerebral hemorrhage are frequently observed after corrective surgery[32].

Concerning peri-operative management, duration of cardiopulmonary bypass, duration of hospital stay and postoperative complications have been found to explain approximately 5% of the variance in development in earlier research[33, 34]. Other intra-operative predictors may be aortic clamping time[35, 36], use of deep hypothermia and circulatory arrest[37-41] and use of allogenic blood[42, 43]. Other post-operative predictors may be duration of ventilation and postoperative cardiac markers such as lactate[44], troponin[45], creatine kinase[46] and creatine kinase-MB fraction[47]. Furthermore, time point of surgery might be an important predictor, with more neurological anomalies observed after corrective surgery during the neonatal period as compared to surgery later in infancy[48]. Beside medical aspects related to the heart defect, patient-related variables such as gender, lower birth weight, presence of genetic/phenotypical anomalies, educational status of the mother and ethnicity explained as much as 30% of the variance in development in earlier research[13, 49].

Importantly, most studies investigating the development of children with CHD are cross-sectional and only few studies have observed the development of children longitudinally and systematically during the first years of life. In one such study, Mussatto and colleagues investigated 99 children (19 of whom had genetic syndromes) with different CHDs (34 univentricular physiology, 65 biventricular physiology) every 6 months, during the first three years of life[50]. In a mixed models analysis, no significant change in cognitive and language development, as assessed with the Bayley Scales of Infant Development (BSID-III) 3-d Edition[51], was observed for participants without genetic syndromes, pointing to a developmental pace comparable to that of healthy infants, even though the majority of children had average to low scores. Motoric scores significantly improved across time, implicating that deficits could be compensated to a certain extent by the developing brain. Children with genetic syndromes showed a decline of cognitive scores, which implies delayed development, and no significant changes in language and motoric scores. This study

adds crucial insights into the dynamics of early development in children with CHD, but more studies are needed that shed light on developmental trajectories, carefully discerning the multitude of potential predictors. Multilevel analysis can be seen as a particularly useful approach for the investigation of development across time, as initial levels of functioning, intraindividual change over time, and individual differences in initial functioning and rates of change can be efficiently modeled[52].

Another gap in research is the role of environmental predictors for the development of children with CHD, for instance the relationship between primary caregiver and child. The concept of “sensitive responsivity” introduced by Ainsworth[53] is a well-established predictor for the cognitive development of healthy children and an increasing number of studies points to the relevance of this concept for development in medically vulnerable groups. In one such study, premature infants had lower cognitive outcomes than full-term infants if parents provided low structuring, but similar outcomes when they provided high structuring[54], which supports the diathesis–stress model[55]. Complicating the role of parenting influences on cognitive development is the fact that not all children are equally affected by their environment. According to the differential susceptibility hypothesis, susceptibility to parenting may depend on child temperament or other individual characteristics, while this susceptibility can be advantageous (in the case of a positive environment) or disadvantageous (in the case of a negative environment)[56]. The study on preterm infants supported this hypothesis: babies with highly reactive temperaments had lower cognitive functioning when little structuring was provided by their mothers, but they had higher cognitive functioning when maternal structuring was high. This association between structuring and cognitive functioning was not found in infants with average reactivity. As premature babies share crucial characteristics with children with CHD concerning their neurological fingerprint, such as brain maturation and white matter injury[29], a similar pattern might be observed in the population of children with CHD. When it comes to temperament, studies in children with CHD are rare. One study showed that children with univentricular physiology show a more difficult temperament (negative mood, more difficult to soothe) at 3 months, when compared to

children with biventricular physiology or healthy controls[57]. Children with biventricular physiology were similar in temperament to healthy controls, but differences between biventricular physiologies (TGA, TOF and VSD) were not investigated.

Aims

The aim of the current study is to investigate long-term early development of children with different congenital heart defects during the first three years of life. We will include children with two different cyanotic heart defects (TGA, TOF) and one acyanotic heart defect (VSD). We will measure cognitive, language and motoric development at 12, 24 and 36 months. We expect clinically relevant developmental delays at ages 12, 24 and 36 months and expect that delays will be significantly higher in children with cyanotic heart defects than in children with an acyanotic heart defect. Furthermore, we hypothesize that developmental delays decline over the course of the first three years. We will investigate predictors for differential developmental pathways, in order to add insight to the etiology of developmental delays and potential risk and protective factors. Specifically, we will look at medical and patient-related predictors. In addition, we will investigate the quality of parenting between primary caregiver and the child as environmental predictor moderated by child temperament. We expect that these predictors will explain a clinically relevant amount of variance at each time point and development from one time point to the next.

METHODS AND ANALYSIS

This study is a single-center prospective cohort study with three groups (TGA, TOF and VSD). Written informed consent will be obtained from all participants. The primary outcome (cognitive, motoric and language development) will be assessed at ages 12, 24 and 36 months; the secondary outcome measure death will be derived from patient files during the course of the study. The secondary outcome measure child temperament will be measured at age 12 months. For a flow chart showing the inclusion process and measurement time points, see Fig. 1.

Participants

The study population comprises children who undergo corrective surgery for TGA, TOF or VSD before the age of 10 months at the department of congenital heart disease / pediatric cardiology at a specialized heart center in Germany. Participating families will be recruited during the hospital stay for corrective surgery via their attending physicians or can also be referred by resident family physicians or cardiologists. Participation is voluntary; compensation for travel costs will be provided.

Inclusion criteria

- Diagnosis of TGA, TOF or VSD
- Corrective surgery at ≤ 10 months
- One parent a native speaker of German

Exclusion criteria

- Genetic syndromes (except for microdeletion syndrome 22Q11) or phenotypic anomalies that might influence the cognitive/motoric development (e.g., trisomy 21, 22Q deletion spectrum).
- Birth weight under 2.5 kg
- Gestational age of less than 37 weeks
- Drug/alcohol abuse/dependence in the history of the mother
- Reanimation with a duration of ≥ 5 minutes before the age of 12 months

Procedure

Assessment of eligibility, inclusion and baseline measures

Parents of children with TGA, TOF or VSD will be approached during their child's hospital stay for corrective surgery. Inclusion and exclusion criteria will be checked by the study physician. If eligible for participations, parents will receive study information (written, oral) from their attending physician. If they decide to participate, written informed consent will be obtained. Parents will then be contacted by telephone by a study nurse after release of the child from hospital in order to make the first appointment at the child's age of 12 months. If

parents are interested but undecided about participation, they will be contacted by the study nurse after hospital discharge and receive additional study information. Open questions will be answered by the study nurse, physician or psychologist. If parents decide to participate, the first appointment will be scheduled at age 12 months and informed consent will be obtained at the beginning of that appointment. At baseline, the following pre-operative variables will be registered: gender, birth weight, birth length, gestational age, Apgar score (0, 5, 10 minutes), comorbidities and time of CHD diagnosis. The following peri-operative variables will be registered: age in months at surgery, duration of surgery, duration of perfusion, aortic cross clamping time, use of allogeneic blood, hypothermia and cardiac markers (lactate, troponin, CK, CK-MB). As indicators of the post-operative course, re-operations, secondary chest closure, ventilation time, time-point of extubation, re-intubation after surgery, duration of hospital stay, neurological events and resuscitation are registered. In the case of pre-operative resuscitation, the neuronal markers NSE and S100 β are registered directly after resuscitation, 24 hours, 48 hours and 72 hours after.

Measurement time points

At time 0 (T0, hospital stay for corrective surgery), medical information will be derived from patient files. At T1 (12 months), parents will fill out questionnaires on demographic variables and child temperament. After that, development of the child will be assessed and the video observation will be conducted. At ages 24 and 36 months (T2, T3), the second and third developmental assessment will be conducted, respectively. At each developmental assessment, additional medical information will be registered based on patient files and the examination records of the child's general practitioners (current weight, length, medical events and symptoms), and information about post-acute rehabilitation care and utilization of early support services for the child will be assessed by a questionnaire developed by the research team.

Measurements

Primary outcome measure

Cognitive, language and motoric development will be assessed with the Bayley Scales of Infant Development (BSID-III) 3-d Edition[51] at ages 12, 24 and 36 months. The BSID-III is an internationally recognized developmental assessment tool with a large normative sample of N=1009 for children between the ages of 16 days to 42 months and 15 days. During this test, the child has to solve different tasks with ascending difficulty in a playful manner. The BSID-III comprises 5 subtests: fine and gross motoric skills, receptive and expressive language, and cognition. The starting point is age-dependent; the number of tasks and ending point depend on the individual performance of the child. Assessment time is approximately 60 to 90 minutes. The language and motoric subtests can be summarized into one score each (language and motoric skills, respectively).

Secondary outcome measures

Death

Death of participating children will be registered as secondary outcome measure throughout the study.

Child temperament

Child temperament at 12 months will be assessed with the Infant Behavior Questionnaire-Revised, Short Version (IBQ-R-SV), which is a 91 item questionnaire with good psychometric properties[58].

Video observation

At age 12 months, a free-play video observation will be conducted with the primary caregiver and the child. Toys (rubber snake, bubbles, building blocks, a cloth, stacking rings) will be placed on a blanket on the floor and the parent will be instructed to spend time with their child during the upcoming 20 minutes. The interaction is recorded with a digital video camera and coded by two independent raters using the "Emotional Availability Scales"[59], which describe the quality of the interaction on several dimensions: sensitivity, structuring, intrusion and hostility of the primary caregiver, as well as child responsivity, and child inclusion of the primary caregiver.

Data handling

Study participant numbers will be used on all documentation to ensure confidentiality. All electronic study-related information will be stored on hospital servers in folders, to which only members of the research team have access. One pass-word protected file linking study participant number and patient identification will be stored separately. On paper study information will be kept in locked cabinets with restricted access. Data will be archived for 15 years after completion of data collection. Data entry will be conducted in duplicate, in order to check for data entry mistakes. Principal and co-investigators will have access to final data files. Authorship of study reports will be assigned according to contribution to design, conduction, data analysis, interpretation and reporting of the results in writing and oral presentation. Study participants and funding institutions will be informed of the results at the end of the study period.

Statistical analyses

Power analysis and sample size

An a priori sample size calculation was performed using G*Power for F-test for Repeated Measures ANOVAs with between-within interaction. Effect sizes for our patient and age group could not be inferred from earlier studies or meta-analyses. Based on clinical observation, we expect small to medium effects. We therefore specified an estimated effect size of Cohen's $f=0.15$, which corresponds to a Cohen's d of 0.3. Alpha error probability was set to 0.0125 to correct for multiple testing (Bonferroni correction), as there are three subscales of the primary outcome measure (cognitive, language and motoric development). Accordingly, significant results with regard to one, two or three of the subscales will reflect true effects. Power was set to 0.80 to detect differences between time points (three measures, three groups, nonsphericity correction of 1). This results in an estimation of the total sample size of 123, or 41 per group. Calculating loss to follow up of 20%, we strive to include 180 infants after corrective surgery, resulting in 40-50 complete participants in each of the 3 CHD groups.

Analyses plan

Primary analyses

Frequency and severity of developmental delays will be described by proportions of mean values. In order to investigate differences between groups (TGA, TOF, VSD) across time (12, 24, 36 months), repeated measure analyses will be conducted with cognitive, motoric and language scores as dependent variables. Time will be entered as within-subjects factor and group as between-subjects factor. Time point of surgery will be entered as covariate. Multiple regressions will be applied for the analysis of medical, person-related and environmental predictors of cognitive, motoric and language scores at each measurement time point.

Secondary analyses

In order to investigate if the three groups (TGA, TOF, VSD) differ in temperament at T1 (12 months), exploratory analysis will be conducted by applying an analysis of covariance, with group (TGA, TOF, VSD) as factor and potentially confounding variables (time point of surgery, gender) entered as covariates.

In order to analyze differential developmental trajectories of the three groups (TGA, TOF, VSD) across time, multilevel modelling will be used with the goal to investigate differences in inter-individual variability (rates of change) and potential predictors influencing individual trajectories.

Time point, cause and circumstances of death will be described and if necessary considered for further analyses.

ETHICS AND DISSEMINATION

The study has been approved by the Medical Ethics Committee Charité Mitte (N. EA2/118/12) on 14 July 2016 and registered with the German Clinical Trials Register (DRKS-ID: DRKS00011006), which is a Primary Registry in the WHO Registry Network, on 18 November 2016. Parents are informed about the option to be debriefed about BSID-III results after each assessment, about the results of the study and that they can withdraw from the

study at any time. Results will be disseminated in peer-reviewed journals and presented at conferences.

CONTRIBUTORS

HF, CP and KS made substantial contributions to the conception or design of the work. HF and CP contributed equally to protocol drafting and protocol editing. KS, LMR and FB reviewed the protocol and made amendments. All authors critically reviewed and approved the final version. All authors agree to be accountable for all aspects of the work.

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COMPETING INTERESTS STATEMENT

None declared.

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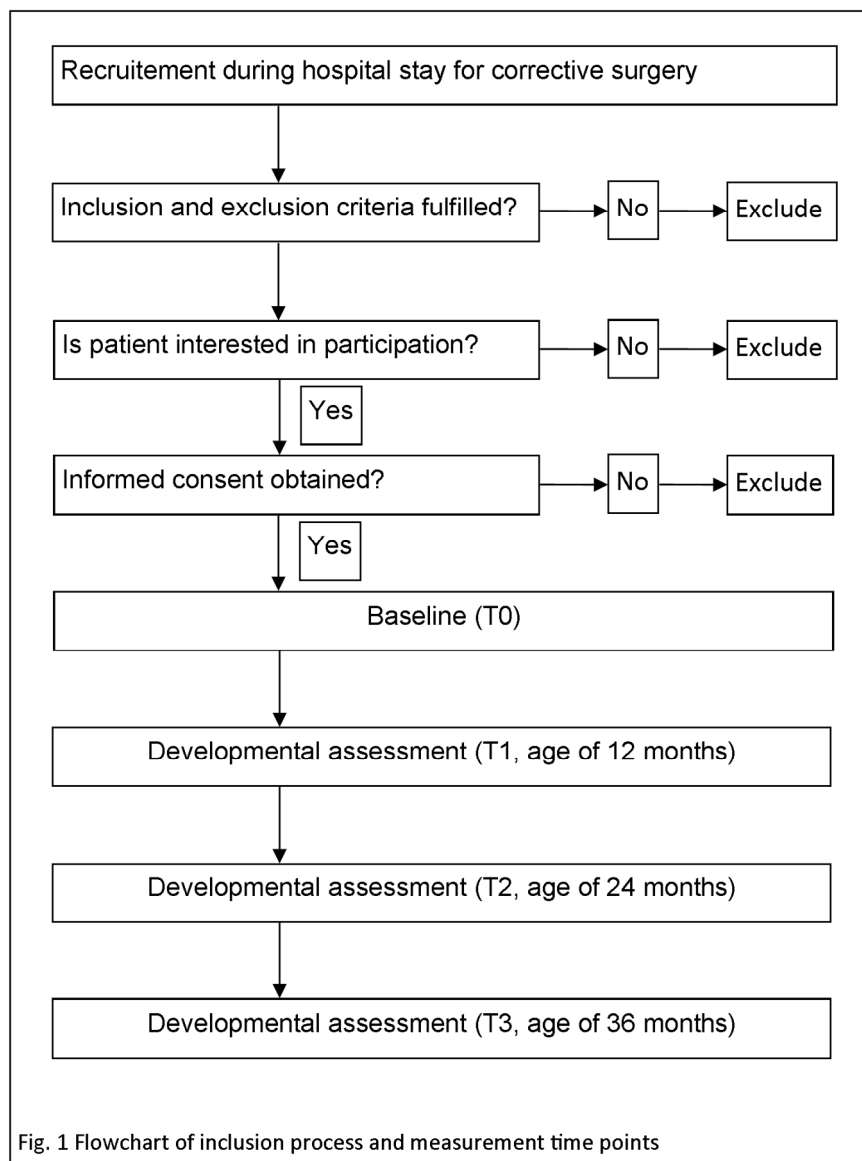
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Long-term early development research in congenital heart disease (LEADER-CHD): A study protocol for a prospective cohort observational study investigating the development of children after surgical correction for congenital heart defects during the first three years of life



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Long-term early development research in congenital heart disease (LEADER-CHD): A study protocol for a prospective cohort observational study investigating the development of children after surgical correction for congenital heart defects during the first three years of life

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ABSTRACT

Introduction

Congenital heart disease is the most common birth defect. Studies on the development of children with CHD point towards deficits in motoric, cognitive and language development. However, most studies are cross-sectional and there is a gap in the knowledge concerning developmental trajectories, risk and protective factors and a lack of research concerning environmental predictors. Specifically, no studies have so far considered the importance of early caregiving experiences and child temperament for the development of children with CHD.

Methods

In a single-center prospective cohort study, cognitive, motoric and language development of 180 children after corrective surgery for a simple transposition of the great arteries (TGA), tetralogy of Fallot (TOF) or ventricular septal defect (VSD) will be assessed at ages 12, 24 and 36 months with the Bayley Scales of Infant Development 3-d Edition (BSID-III). At age 12 months, a free-play video observation will be conducted to investigate the relationship between primary caregiver and child, and child temperament will be assessed with the Infant Behavior Questionnaire - Revised Short Version (IBQ-R-SV). Medical information will be obtained from patient records, demographic information via questionnaires.

Analysis

Frequency and severity of developmental delays will be reported descriptively. Differences between groups (TGA, TOF, VSD) will be subjected to repeated measure analysis across time points. Multiple regressions will be applied for the analysis of predictors at each time point. For the analysis of differential developmental trajectories, mixed model analysis will be applied.

Ethics and dissemination

The study has been approved by the local medical ethics committee. Written informed consent will be obtained from all participants. Parents have the option to be debriefed about BSID-III results after each assessment and about the study results after project completion. Results will be disseminated in peer-reviewed journals.

Trial registration

The study was prospectively registered with the German Clinical Trials Register.

STRENGTH AND LIMITATIONS OF THIS STUDY

- No brain MRI will be conducted at any time point; postnatal MRI of the brain might provide valuable insights into the relationship between alterations of the central nervous system, perioperative complications and developmental delays, but is beyond the scope of this study.
- The longitudinal study design allows the investigation of developmental trajectories across different time points and of specific predictors for differential trajectories.
- By investigating 3 CHD groups (TGA, TOF, VSD), valuable information can be derived for distinctive patterns of development dependent on diagnosis.
- To our knowledge, this interdisciplinary study is the first to investigate the role of quality of caregiver-child interaction for development in this patient group, which has important theoretical implications and is highly relevant for the development of secondary prevention programs.

KEY WORDS

Congenital Heart Disease, Transposition of the Great Arteries, Tetralogy of Fallot, Ventricular Septal Defect, Cyanotic Heart Defect, Acyanotic Heart Defect, Development, Motoric Development, Language Development, Cognitive Development, Parenting, Temperament, Quality of Caregiving, Primary Caregiver

INTRODUCTION

Background and rationale

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3 Congenital heart disease (CHD) is the most common birth defect and the incidence ranges
4 from 19 to 75 per 1000 live births worldwide[1]. During the past years, medical care for
5 children with CHD has significantly improved, due to scientific progress leading to
6 advancement of early diagnostics[2-5] and technical possibilities[6, 7]. This has led to
7 increased survival rates[8, 9]. In Germany, more than 6500 children are born with a CHD
8 each year, which is approximately every hundredth child, and more than 90% reach
9 adulthood, while mortality has fallen by 60% since 1990[10]. There is now a growing
10 research interest in morbidity and quality of life of these patients[11, 12]. Studies on the
11 development of children with CHD generally point towards deficits in motoric, cognitive and
12 language development[13-18], which are mostly weak to moderate and often combined[19].
13 Even though developmental delays tend to decline with time[13], they are still observed
14 many years after successful surgery and potentially manifest themselves in learning or
15 behavioral difficulties[20, 21], which implies that they are not transient in nature. Children
16 with cyanotic heart defects, such as transposition of the great arteries (TGA) or tetralogy of
17 Fallot (TOF) have been found to have worse developmental outcomes than children with
18 acyanotic heart defects, such as ventricular septal defects (VSD), in several studies[22-26],
19 while other studies did not find systematic differences between TGA, TOF, or VSD, for
20 instance after taking demographic, preoperative, and operative variables into account[15].
21 These contrasting results point towards a complex relationship between physiological
22 characteristics of the heart defect, neurological sequelae, therapeutic necessities and
23 patient-related factors when it comes to future development[27, 28].

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25 On a neurological level, the etiology of developmental delays in children with CHD is
26 complex, concerning the specific time point as well as the mechanism that leads to
27 alterations[29]. Already pre-operatively, certain abnormalities of the central nervous system
28 can be observed, in particular less mature macro- and microstructural brain development and
29 lower brain volume[28]. These changes can be attributed to reduced oxygenation and
30 perfusion, while the relative contribution depends on the specific defect[30]. Decelerated
31 brain development is a predisposing factor for white matter injury, which is often present in
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newborns with CHD[31]. In addition, infarction, ischemic strokes and cerebral hemorrhage are frequently observed after corrective surgery[32].

Concerning peri-operative management, duration of cardiopulmonary bypass, duration of hospital stay and postoperative complications have been found to explain approximately 5% of the variance in development in earlier research[33, 34]. Other intra-operative predictors may be aortic clamping time[35, 36], use of deep hypothermia and circulatory arrest[37-41] and use of allogenic blood[42, 43]. Other post-operative predictors may be duration of ventilation and postoperative cardiac markers such as lactate[44], troponin[45], creatine kinase[46] and creatine kinase-MB fraction[47]. Furthermore, time point of surgery might be an important predictor, with more neurological anomalies observed after corrective surgery during the neonatal period as compared to surgery later in infancy[48] and Eisenmenger pathophysiology as a complication of uncorrected VSD later in life[49]. Beside medical aspects related to the heart defect, patient-related variables such as gender, lower birth weight, presence of genetic/phenotypical anomalies, educational status of the mother and ethnicity explained as much as 30% of the variance in development in earlier research[13, 50].

Importantly, most studies investigating the development of children with CHD are cross-sectional and only few studies have observed the development of children longitudinally and systematically during the first years of life. In one such study, Mussatto and colleagues investigated 99 children (19 of whom had genetic syndromes) with different CHDs (34 univentricular physiology, 65 biventricular physiology) every 6 months, during the first three years of life[51]. In a mixed models analysis, no significant change in cognitive and language development, as assessed with the Bayley Scales of Infant Development (BSID-III) 3-d Edition[52], was observed for participants without genetic syndromes, pointing to a developmental pace comparable to that of healthy infants, even though the majority of children had average to low scores. Motoric scores significantly improved across time, implicating that deficits could be compensated to a certain extent by the developing brain. Children with genetic syndromes showed a decline of cognitive scores, which implies

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3 delayed development, and no significant changes in language and motoric scores. This study
4 adds crucial insights into the dynamics of early development in children with CHD, but more
5 studies are needed that shed light on developmental trajectories, carefully discerning the
6 multitude of potential predictors. Multilevel analysis can be seen as a particularly useful
7 approach for the investigation of development across time, as initial levels of functioning,
8 intraindividual change over time, and individual differences in initial functioning and rates of
9 change can be efficiently modeled[53].

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17 Another gap in research is the role of environmental predictors for the development of
18 children with CHD, for instance the relationship between primary caregiver and child. The
19 concept of “sensitive responsivity” introduced by Ainsworth[54] is a well-established predictor
20 for the cognitive development of healthy children and an increasing number of studies points
21 to the relevance of this concept for development in medically vulnerable groups. In one such
22 study, premature infants had lower cognitive outcomes than full-term infants if parents
23 provided low structuring, but similar outcomes when they provided high structuring[55], which
24 supports the diathesis–stress model[56]. Complicating the role of parenting influences on
25 cognitive development is the fact that not all children are equally affected by their
26 environment. According to the differential susceptibility hypothesis, susceptibility to parenting
27 may depend on child temperament or other individual characteristics, while this susceptibility
28 can be advantageous (in the case of a positive environment) or disadvantageous (in the case
29 of a negative environment)[57]. The study on preterm infants supported this hypothesis:
30 babies with highly reactive temperaments had lower cognitive functioning when little
31 structuring was provided by their mothers, but they had higher cognitive functioning when
32 maternal structuring was high. This association between structuring and cognitive functioning
33 was not found in infants with average reactivity. As premature babies share crucial
34 characteristics with children with CHD concerning their neurological fingerprint, such as brain
35 maturation and white matter injury[29], a similar pattern might be observed in the population
36 of children with CHD. When it comes to temperament, studies in children with CHD are rare.
37 One study showed that children with univentricular physiology show a more difficult

temperament (negative mood, more difficult to soothe) at 3 months, when compared to children with biventricular physiology or healthy controls[58]. Children with biventricular physiology were similar in temperament to healthy controls, but differences between biventricular physiologies (TGA, TOF and VSD) were not investigated.

Aims

The aim of the current study is to investigate long-term early development of children with different congenital heart defects during the first three years of life. We will include children with two different cyanotic heart defects (TGA, TOF) and one acyanotic heart defect (VSD), who undergo corrective surgery before the age of 10 months. We will measure cognitive, language and motoric development at 12, 24 and 36 months. We expect clinically relevant developmental delays at ages 12, 24 and 36 months and expect that delays will be significantly higher in children with cyanotic heart defects than in children with an acyanotic heart defect. Furthermore, we hypothesize that developmental delays decline over the course of the first three years. We will investigate predictors for differential developmental pathways, in order to add insight to the etiology of developmental delays and potential risk and protective factors. Specifically, we will look at medical and patient-related predictors. In addition, we will investigate the quality of parenting between primary caregiver and the child as environmental predictor moderated by child temperament. We expect that these predictors will explain a clinically relevant amount of variance at each time point and development from one time point to the next.

METHODS AND ANALYSIS

This study is a single-center prospective cohort study with three groups (TGA, TOF and VSD). Written informed consent will be obtained from all participants. The primary outcome (cognitive, motoric and language development) will be assessed at ages 12, 24 and 36 months; the secondary outcome measure death will be derived from patient files during the course of the study. The secondary outcome measure child temperament will be measured at age 12 months. For a flow chart showing the inclusion process and measurement time points, see Fig. 1.

Participants

The study population comprises children who undergo corrective surgery for TGA, TOF or VSD before the age of 10 months at the department of congenital heart disease / pediatric cardiology at a specialized heart center in Germany. Participating families will be recruited during the hospital stay for corrective surgery via their attending physicians or can also be referred by resident family physicians or cardiologists. Participation is voluntary; compensation for travel costs will be provided.

Inclusion criteria

- Diagnosis of TGA, TOF or VSD
- Corrective surgery at ≤ 10 months
- One parent a native speaker of German

Exclusion criteria

- Genetic syndromes (except for microdeletion syndrome 22Q11) or phenotypic anomalies that might influence the cognitive/motoric development (e.g., trisomy 21, 22Q deletion spectrum).
- Birth weight under 2.5 kg
- Gestational age of less than 37 weeks
- Drug/alcohol abuse/dependence in the history of the mother
- Reanimation with a duration of ≥ 5 minutes before the age of 12 months

Procedure

Assessment of eligibility, inclusion and baseline measures

Parents of children with TGA, TOF or VSD will be approached during their child's hospital stay for corrective surgery. Inclusion and exclusion criteria will be checked by the study physician. If eligible for participations, parents will receive study information (written, oral) from their attending physician. If they decide to participate, written informed consent will be obtained. Parents will then be contacted by telephone by a study nurse after release of the

child from hospital in order to make the first appointment at the child's age of 12 months. If parents are interested but undecided about participation, they will be contacted by the study nurse after hospital discharge and receive additional study information. Open questions will be answered by the study nurse, physician or psychologist. If parents decide to participate, the first appointment will be scheduled at age 12 months and informed consent will be obtained at the beginning of that appointment. At baseline, the following pre-operative variables will be registered: gender, birth weight, birth length, gestational age, Apgar score (0, 5, 10 minutes), comorbidities and time of CHD diagnosis. The following peri-operative variables will be registered: age in months at surgery, duration of surgery, duration of perfusion, aortic cross clamping time, use of allogeneic blood, hypothermia, cardiac markers (lactate, troponin, CK, CK-MB) and type, dose and duration of anesthetics, analgesics and sedatives. As indicators of the post-operative course, re-operations, secondary chest closure, ventilation time, time-point of extubation, re-intubation after surgery, duration of hospital stay, neurological events (including hypoxic events, i.e., cerebral infarction, global cerebral ischemia), last CO₂ level, oxygen saturation at discharge and resuscitation are registered. In the case of pre-operative resuscitation, the neuronal markers NSE and S100 β are registered directly after resuscitation, 24 hours, 48 hours and 72 hours after.

Measurement time points

At time 0 (T₀, hospital stay for corrective surgery), medical information will be derived from patient files. At T₁ (12 months), parents will fill out questionnaires on demographic variables and child temperament. After that, development of the child will be assessed and the video observation will be conducted. At ages 24 and 36 months (T₂, T₃), the second and third developmental assessment will be conducted, respectively. At each developmental assessment, additional medical information will be registered based on patient files and the examination records of the child's general practitioners (current weight, length, medical events and symptoms), and information about post-acute rehabilitation care and utilization of early support services for the child will be assessed by a questionnaire developed by the research team.

Measurements

Primary outcome measure

Cognitive, language and motoric development will be assessed with the Bayley Scales of Infant Development (BSID-III) 3-d Edition[52] at ages 12, 24 and 36 months. The BSID-III is an internationally recognized developmental assessment tool with a large normative sample of N=1009 for children between the ages of 16 days to 42 months and 15 days. During this test, the child has to solve different tasks with ascending difficulty in a playful manner. The BSID-III comprises 5 subtests: fine and gross motoric skills, receptive and expressive language, and cognition. The starting point is age-dependent; the number of tasks and ending point depend on the individual performance of the child. Assessment time is approximately 60 to 90 minutes. The language and motoric subtests can be summarized into one score each (language and motoric skills, respectively).

Secondary outcome measures

Death

Death of participating children will be registered as secondary outcome measure throughout the study.

Child temperament

Child temperament at 12 months will be assessed with the Infant Behavior Questionnaire-Revised, Short Version (IBQ-R-SV), which is a 91 item questionnaire with good psychometric properties[59].

Video observation

At age 12 months, a free-play video observation will be conducted with the primary caregiver and the child. Toys (rubber snake, bubbles, building blocks, a cloth, stacking rings) will be placed on a blanket on the floor and the parent will be instructed to spend time with their child during the upcoming 20 minutes. The interaction is recorded with a digital video camera and coded by two independent raters using the "Emotional Availability Scales"[60], which

describe the quality of the interaction on several dimensions: sensitivity, structuring, intrusion and hostility of the primary caregiver, as well as child responsivity, and child inclusion of the primary caregiver.

Data handling

Study participant numbers will be used on all documentation to ensure confidentiality. All electronic study-related information will be stored on hospital servers in folders, to which only members of the research team have access. One pass-word protected file linking study participant number and patient identification will be stored separately. On paper study information will be kept in locked cabinets with restricted access. Data will be archived for 15 years after completion of data collection. Data entry will be conducted in duplicate, in order to check for data entry mistakes. Principal and co-investigators will have access to final data files. Authorship of study reports will be assigned according to contribution to design, conduction, data analysis, interpretation and reporting of the results in writing and oral presentation. Study participants and funding institutions will be informed of the results at the end of the study period.

Statistical analyses

Power analysis and sample size

An a priori sample size calculation was performed using G*Power for F-test for Repeated Measures ANOVAs with between-within interaction. Effect sizes for our patient and age group could not be inferred from earlier studies or meta-analyses. Based on clinical observation, we expect small to medium effects. We therefore specified an estimated effect size of Cohen's $f=0.15$, which corresponds to a Cohen's d of 0.3. Alpha error probability was set to 0.0125 to correct for multiple testing (Bonferroni correction), as there are three subscales of the primary outcome measure (cognitive, language and motoric development). Accordingly, significant results with regard to one, two or three of the subscales will reflect true effects. Power was set to 0.80 to detect differences between time points (three measures, three groups, nonsphericity correction of 1). This results in an estimation of the

total sample size of 123, or 41 per group. Calculating loss to follow up of 20%, we strive to include 180 infants after corrective surgery, resulting in 40-50 complete participants in each of the 3 CHD groups.

Analyses plan

Primary analyses

Frequency and severity of developmental delays will be described by proportions of mean values. In order to investigate differences between groups (TGA, TOF, VSD) across time (12, 24, 36 months), repeated measure analyses will be conducted with cognitive, motoric and language scores as dependent variables. Time will be entered as within-subjects factor and group as between-subjects factor. Time point of surgery will be entered as covariate. Multiple regressions will be applied for the analysis of medical, person-related and environmental predictors of cognitive, motoric and language scores at each measurement time point.

Secondary analyses

In order to investigate if the three groups (TGA, TOF, VSD) differ in temperament at T1 (12 months), exploratory analysis will be conducted by applying an analysis of covariance, with group (TGA, TOF, VSD) as factor and potentially confounding variables (time point of surgery, gender) entered as covariates.

In order to analyze differential developmental trajectories of the three groups (TGA, TOF, VSD) across time, multilevel modelling will be used with the goal to investigate differences in inter-individual variability (rates of change) and potential predictors influencing individual trajectories.

Time point, cause and circumstances of death will be described and if necessary considered for further analyses.

ETHICS AND DISSEMINATION

The study has been approved by the Medical Ethics Committee Charité Mitte (N. EA2/118/12) on 14 July 2016 and registered with the German Clinical Trials Register (DRKS-

ID: DRKS00011006), which is a Primary Registry in the WHO Registry Network, on 18 November 2016. Parents are informed about the option to be debriefed about BSID-III results after each assessment, about the results of the study and that they can withdraw from the study at any time. Results will be disseminated in peer-reviewed journals and presented at conferences.

CONTRIBUTORS

HF, CP and KS made substantial contributions to the conception or design of the work. HF and CP contributed equally to protocol drafting and protocol editing. KS, LMR and FB reviewed the protocol and made amendments. All authors critically reviewed and approved the final version. All authors agree to be accountable for all aspects of the work.

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COMPETING INTERESTS STATEMENT

None declared.

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FIGURE LEGENDS

Fig. 1 Flowchart of inclusion process and measurement time points

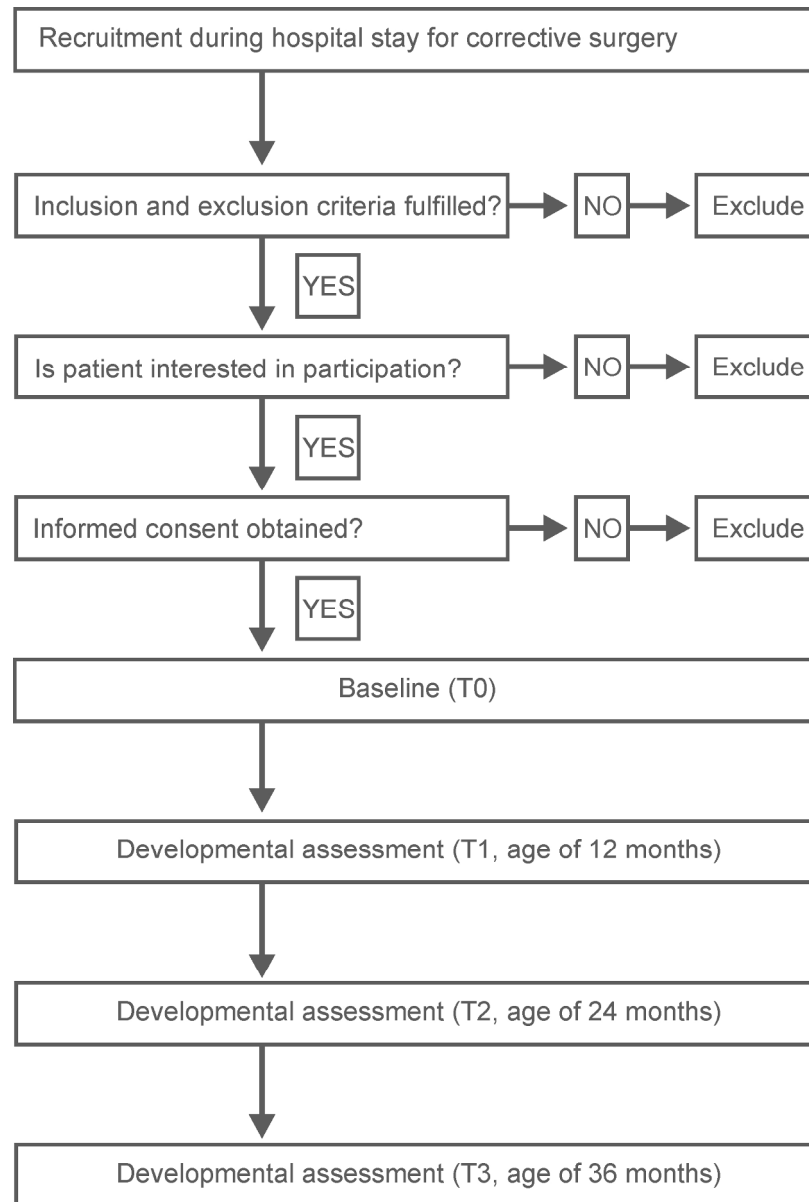


Fig. 1 Flowchart of inclusion process and measurement time points

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